PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 21A024712WO4M	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IT 03/00400	International filing date *(day/month/year)* 27.06.2003	Priority date *(day/month/year)* 06.09.2002
International Patent Classification (IPC) or both national classification and IPC A23L1/304		
Applicant AGRISTUDIO S.R.L. .et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
05.04.2004	18.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Rooney, K Telephone No. +31 70 340-3931

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IT 03/00400

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-16 as originally filed

Claims, Numbers

1-9, 12-25 received on 21.02.2005 with letter of 21.02.2005

Drawings, Figures

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-9, 22-25 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-9, 22-25
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9,22-25
Industrial applicability (IA)	Yes:	Claims	1-9,22-25
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item IV
Lack of unity of invention

1. Reference is made to the following document:

D1: WO 00/53032 A (CIRIBOLLA ANTONIO ;AGRISTUDIO S R L (IT)) 14 September 2000 (2000-09-14)

2. This Authority considers that there are 2 inventions covered by the claims indicated as follows:

I: Claims 1-9 directed to preparing a metal chelate having the formula (CH3SCH2CH2CH(OH)COO)2M.nH2O and use in human and animal nutrition where M is a bivalent metal cation chosen from the group of Mg Ca Mn Co Cu Zn and Fe and n is the number of complexed water molecules.

II: Claims 22-25 directed to a stable aqueous solution of iron (III) or chrome (III) complex with two or more than two molecules of hydroxy methionine analog, method for its preparation and the use thereof.

3. The reasons for which the inventions are not so linked as to form a single general inventive concept, as required by Rule 13.1 PCT, are as follows:

The problem underlying the present invention is the provision of trace metal ions to humans and animals in a easily assimilable and bioavailable form.

The solution proposed by invention 1 consists of a method involving the delivery of bivalent metal ions to humans and animals by complexation with methionine hydroxy analog. The features of this invention include complexation of bivalent metal ions to two of the methionine hydroxy analog molecules.

The solution proposed by invention 2 consists of a method involving the delivery of trivalent metal ions to humans and animals by complexation with methionine hydroxy analog. The features of this invention include complexation of trivalent iron or chrome to two or more of the methionine hydroxy analog molecules.

The special technical feature in the sense of Rule 13 PCT which links the subject-matter of the different inventions is the use of complexation of metal ions to methionine hydroxy analog in human and animal nutrition in order to resolve the above stated problems. This feature as well as the general problem is known from the document WO00/53032 (see whole document) which discloses an alimentary product for humans and animals which comprises bivalent metal ions complexed to 2 molecules of methionine hydroxy analog and therefore can no longer form the single inventive concept.

Additional fees have been paid for searching and examining the subject-matter of the second invention.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: WO 00/53032 A (CIRIBOLLA ANTONIO ;AGRISTUDIO S R L (IT)) 14 September 2000 (2000-09-14)
D2: WO 02/30216 A (HICKMAN DAN S ; BEVANS BASIL D (US); BUNTING L DWAIN (US)) 18 April 2002 (2002-04-18)

2. Novelty

Invention 1

The present application meets the requirements of Article 33 (1) PCT because the subject-matter of claims 1,5,6 and 7 is new in the sense of Article 33 (2) PCT.

Invention 2

The present application meets the requirements of Article 33 (1) PCT because the subject-matter of claims 22-25 is new in the sense of Article 33 (2) PCT with respect to the available prior art.

3. Inventive Step

Invention 1

The present application does not meet the requirements of Article 33 (3) PCT because the subject-matter of independent claims 1,5,6 and 7 does not involve an inventive step.

The subject-matter of claim 1 differs from the teaching of the document D1 (see D1: the whole document) in that the compound is administered to human beings rather than to any other type of animal. However, given that one objective of the present application is to provide humans with compounds which are already known as suitable for animals, it seems unsurprising and uninventive that one might modify the document D1 and use the additive in human nutrition. Furthermore, there is no indication in the application as filed that feeding to humans versus feeding to animals has produced any surprising effects.

The subject-matter of claim 5 and 6 differs from the teaching of the document D1 merely in the specification of the number of water molecules which are chelated with the metal compound. The selection of the amount of water molecules however is not linked to any specific technical effect in the application as filed and therefore is unlikely to be a basis for an inventive step.

Regarding the new claim 7 (old claim 9), the document D1 discloses methods of preparing metal chelates having the formula (CH3SCH2CH2CH(OH)COO)2 M. nH20 as above, by reacting for example a soluble bivalent metal salt (carbonate) with methionine hydroxy analog. While the specific iron (II) salt and an alkali salt of the amino acid are not disclosed in the document D1, it seems that the selection of iron is obvious to those skilled in the art in solving the problem of providing such iron chelates and the amino acid is merely a known alternative form generally known to those skilled in the art.

Invention 2

The present application does not meet the requirements of Article 33 (3) PCT because the subject-matter of independent claims 22-25 does not involve an inventive step.

The document D2 discloses a method of producing a hydroxy methionine analog

composition which may contain reactive iron oxide. The compositions are intended for use in the fields of human and animal nutrition. The methionine and iron oxide are reacted to result in final ratios of 5-15:1. Optionally the metal may be added in such a way that it appears that the composition may be aqueous (see D2; the whole document). The subject-matter of claims 22-25 differs from the teaching of the document D2 merely in details which are not fully specified in that document, namely the oxidation state of the iron found therein and whether it can be considered 'aqueous' per se. The term 'reactive' as used in D2 seems to point toward the oxidation state of II although this state is produced by heating of iron oxide having an oxidation state of III. Therefore the subject-matter of the claims 22-25 can be considered as a selection of features from the prior art which would be obvious to those skilled in the art.

4. Dependent claims

Invention 1

Claims 2-4 relate to mere selections which are clear and evident uses which would be well known to those skilled in the art.

Claims 8-9 relate to features which are standard laboratory practice well known to those skilled in the art and as such do not contribute any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.

AMENDED SET OF CLAIMS

1. Use of at least a metal chelate chosen among those having the general formula (I):

$(CH_3SCH_2CH_2CH(OH)COO)_2M \bullet nH_2O$ (I)

in which: M is a bivalent metal cation chosen from the group comprising: Mg, Ca, Mn, Co, Cu, Zn and Fe, and n is the number of water molecules; for preparing an integrator for administration in human beings nutrition.

2. Use according to claim 1, in which the integrator is administered to patients suffering from a deficiency of metal oligoelements such as Mg, Ca, Mn, Co, Cu, Zn and Fe.

3. Use according to claim 1, in which said at least one metal chelate is chosen from the group comprising:

$(CH_3SCH_2CH_2CH(OH)COO)_2Zn \bullet 2H_2O$;

$(CH_3SCH_2CH_2CH(OH)COO)_2Cu$;

$(CH_3SCH_2CH_2CH(OH)COO)_2Co \bullet 2H_2O$;

$(CH_3SCH_2CH_2CH(OH)COO)_2Mn \bullet 2H_2O$;

$(CH_3SCH_2CH_2CH(OH)COO)_2Ca \bullet 2H_2O$;

$(CH_3SCH_2CH_2CH(OH)COO)_2Mg \bullet 2H_2O$;

$(CH_3SCH_2CH_2CH(OH)COO)_2Fe \bullet 2H_2O$

for preparing an integrator for administration in human nutrition.

4. Use according to claim 3, in which the integrator is administered to patients suffering from a deficiency of metal oligoelements such as: Mg, Ca, Mn, Co, Cu, Zn and Fe.

~~5. Use of at least a metal chelate chosen among those~~

~~having the general formula (I):~~

~~$(CH_3SCH_2CH_2CH(OH)COO)_2M \bullet nH_2O$ (I)~~

~~in which: M is a bivalent metal cation chosen from the group comprising: Mg, Ca, Mn, Co, Cu, Zn and Fe, and n is the number of water molecules, for preparing an integrator for agro-zootechnical nutrition to be administered to monogastric or polygastric animals.~~

~~6. Use according to claim 5, in which the integrator is administered to monogastric or polygastric animals suffering from a deficiency of metal oligoelements such as Mg, Ca, Mn, Co, Cu, Zn and Fe.~~

~~7~~ 5 (Amended). Use of at least one metal chelate selected from the group consisting of: ~~according to claim 5, in which said at least a metal chelate is chosen from the group comprising:~~

$(CH_3SCH_2CH_2CH(OH)COO)_2Zn \bullet 2H_2O$;
$(CH_3SCH_2CH_2CH(OH)COO)_2Cu$;
$(CH_3SCH_2CH_2CH(OH)COO)_2Co \bullet 2H_2O$;
$(CH_3SCH_2CH_2CH(OH)COO)_2Mn \bullet 2H_2O$;
$(CH_3SCH_2CH_2CH(OH)COO)_2Ca \bullet 2H_2O$;
$(CH_3SCH_2CH_2CH(OH)COO)_2Mg \bullet 2H_2O$;
$(CH_3SCH_2CH_2CH(OH)COO)_2Fe \bullet 2H_2O$

for preparing an integrator for agro-zootechnical nutrition to be administered to monogastric and polygastric animals.

~~8. Use according to claim 7, in which the integrator is administered to monogastric or polygastric animals~~ suffering from a deficiency of metal oligoelements such as Mg, Ca, Mn, Co, Cu, Zn and Fe.

6. (New). A metal chelate of formula

$(CH_3SCH_2CH_2CH(OH)COO)_2Fe \bullet 2H_2O$.

~~9~~ 7 (Original). Method for preparing a metal chelate $(CH_3SCH_2CH_2CH(OH)COO)_2Fe \bullet 2H_2O$ comprising a step in which an alkali metal or alkaline-earth metal salt of methionine hydroxy analogue is reacted with a soluble iron (II) salt in water environment.

~~10~~ 8 (Original). Method according to claim ~~9~~ 7, in which the reaction takes place between sodium salt of methionine hydroxy analogue and ferrous sulfate.

~~11~~ 9 (Original). Method according to claim ~~9~~ 7 or ~~10~~ 8, in which iron (II) chelate obtained from the reaction is filtered and washed with water.

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12. Method for preparing a metal vanadium chelate comprising a step in which a vanadium (V) oxide or salt is reacted with a solution of methionine hydroxy analogue.

13. Method according to claim 12, in which vanadium oxide is V_2O_5.

14. Method according to claim 12 or 13, in which the reaction takes place at high temperature and under stirring.

15. Use of metal vanadium chelates prepared according to one of the claims 12 to 14 for preparing an integrator to be administered in human nutrition.

16. Use of metal vanadium chelates prepared according to one of the claims 12 to 14 for preparing an integrator for agro-zootechnical nutrition to be administered to monogastric or polygastric animals.

17. Method for preparing a metal molybdenum chelate comprising a step in which a molybdenum (VI) oxide or salt is reacted with a solution of methionine hydroxy analogue.

18. Method according to claim 17, in which molybdenum oxide is MoO_3.

19. Method according to claim 17 or 18, in which the reaction takes place at high temperature and under stirring.

20. Use of metal molybdenum chelates prepared according to one of the claims 17 to 19 for preparing an integrator to be administered in human nutrition.

21. Use of metal molybdenum chelates prepared according to one of the claims 17 to 19 for preparing an integrator for agro-zootechnical nutrition to be administered to monogastric or polygastric animals.

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22. (Original) Stable aqueous solution of iron (III) or chrome (III) complexes with MHA in which the molar ratio MHA/M(III) is ≥ 2.

23. (Original) Method for preparing a stable aqueous solution according to claim 22, comprising a step in

which methionine hydroxy analogue MHA is reacted with an aqueous solution of a soluble iron (III) or chrome (III) salt.

24. (Original) Use of a stable solution of iron (III) or chrome (III) complexes according to claim 22 for preparing an integrator for administration in human nutrition.

25. (Original) Use of a stable solution of iron (III) or chrome (III) complexes according to claim 22 for preparing an integrator in agro-zootechnical nutrition to be administered to monogastric or polygastric animals.

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